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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,109	01/26/2001	Allan S. Lau	4099-0003.31	8965

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,109	LAU ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,11,39 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,11 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed August 22, 2005 in response to the Office Action of June 27, 2005 is acknowledged and has been entered. Claims 5, 25, 26, 29, 31-34 and 37 have been cancelled. Claim 41 has been added. Claims 1-3, 6-8, 11, 39, 40 and 41 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Priority

This application is a CIP of application 09/657881 and the provisional application 60/152854. Claims that make reference to CrmA will only be granted the priority to the filing date of the instant application which is January 26, 2001.

Claim Rejections - 35 USC § 103

The rejection of claims 1-3, 6-8, 11, 39-40 and newly added claims 41 under 35 U.S.C. 103(a) as being unpatentable over Dixit (U.S. Pat. No. 6,159,712), Lau et al. (U.S.Pat. No. 6,159,712) and Suzuki et al. (Derwent Abstract XP-002170158; see IDS Paper No. 13; JP9-163983-A see PTO 892 translation of full patent included) **is maintained** for reasons of record.

Applicants' arguments and the Offices response are essentially the same of record. Applicants' arguments are: (1) there is no motivation to combine the references, (2) no reasonable expectation of success, (3) no suggestion of the advantages obtained by the combination, (4) that the logic of *in re Kerkhoven* is inapt because the Dixit or Suzuki reference

have not actually demonstrated that transformation of a cell line with an anti-apoptotic protein does in fact enhance cytokine production. Applicants' arguments have been fully considered but are not persuasive for reasons of record.

In response to applicant's argument that there is no suggestion (motivation) to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Suzuki et al. does more than just merely teach the prevention of apoptosis in a cell. The teachings of Susuki et al. are directed to the increase in the ability of a cell to produce useful matter (product), such as cytokines, by preventing apoptosis from killing the cell prematurely. The increased cell life translates into an increased production of the product (see paragraph 0021). The reference teaches the use of a cell line that contains an apoptosis inhibiting gene. The reference suggests the use of anti-apoptosis inhibitor genes, for example Bcl-2, BAG-1, Bcl-XL, Ad.E1b, and CrmA to increase the production of cytokines from cell lines. The reference exemplifies the introduction of Bcl-2 expressing gene into a cell line fore the use of producing increased amounts of antibody (see paragraph 0025). The reference shows that cell lines which have increased production of Bcl-2 are able to grow under low serum culture conditions and show a strong resistance to apoptosis (see paragraph 0052, 0053, and figure 8). Thus the reference teaches that by increasing viability of the cells you will increase the production of a composition from the cell line. Here the reference teaches the production of

useful product (composition such as a cytokine) by keeping the cell lines alive. The reference suggests the use of a handful of anti-apoptotic genes and the reference has shown working examples of one such apoptotic gene in a cell line. Thus, the reference serves as more than a mere general teaching and is a roadmap for using CrmA in a cell line for the production of compositions from the cell.

Dixit V.M. teaches the transformation of MCF7 and BJAB cells (human derived cells line) with a vector encoding Crm-A (see examples 3, 4 and 5). It would have been obvious to one of ordinary skill in the art to utilize the cell line taught by Dixit for the production of useful matter, such as a cytokine, as taught by Suzuki et al. Suzuki et al. also establishes that those cells that contain the apoptosis inhibiting genes produce more protein when compared to cells that do not have the gene insert, the level of protein production doubled at day 7 and tripled at day 14 (see figure 9, Suzuki et al.). In considering the teachings of Dixit and Suzuki et al. one of ordinary skill in the art would have had a high expectation of success in using the cell line of Dixit for the production of useful matter, such as a cytokine, given the teaching of Susuki et al. Thus the combination of Suzuki et al. and Dixit teaches the use of a CrmA expressing cell for the production of useful matter.

In response to applicants arguments that there is no reasonable expectation of success to combine the teachings. This argument is not convincing because the reference of Susuki et al. teaches the use of the anti-apoptotic gene Bcl-2 for the production of a composition (an antibody) at low serum culture conditions. The reference teaches that by increasing the viability of a cell the production of a useful composition from the cell will also increase.

Lau et al. teaches a method of producing a cell that is able to overexpress cytokines wherein the cell comprises a vector containing PKR, and the cytokine expression is stimulated by induction using poly I:C and the priming agent PMA. Overexpression of PKR induced overproduction of the cytokines INF-alpha and INF-beta. The reference shows that interferon production can be stimulated in a PKR expressing cell without the use of a live virus, such as encephalomyocarditis virus (ECMV) (see figure 2). The reference indicates that using ECMV virus to induce interferon production results in the loss of viability of the cells (see column 7, lines 40-46). The loss of viable cells will result in the loss of compound (interferon) production by the cell over time. The reference also teaches that the use of PKR cell lines will result in interferon production after priming and poly I:C treatment that is comparable to the interferon production induced by ECMV (see column 7, lines 25-30). Thus the reference teaches that PKR expressing cells can be stimulated to induce interferon by priming and poly I:C treatment that does not result in the loss of viability of the cell. The increased viability of the cell will lead to increased production of the useful compost ion (interferon) over time.

The ordinary artisan would have a reasonable expectation of success that when combining an anti-apoptotic gene expression in a cell, taught by Susuki et al., with the gene expression of PKR, taught by Lau, in the same cell will result in a cell that will have increased viability when encountering an apoptotic stimulus. The apoptotic stimulus can come from a viral infection or by crosslinking a cell surface receptor. The ordinary artisan would expect that the increased compound production in a cell expressing both the PKR and the anti-apoptotic gene would result in an additive effect of the production of the composition when only one of the genes is expressed in the cell.

In response to the argument that there is no suggestion of the advantages obtained by the combination. It appears applicant is making an argument based on unexpected results. A careful review of the instant specification indicates that such an unexpected result has not been established in the specification. The combination of Bcl-Xl and PKR in a single cell line results in interferon production that is merely additive. Thus applicants have not established a synergistic effect when expressing an anti-apoptotic gene and the PKR gene in a cell line for the production of interferon. Figure 1 in the specification indicates that when a virus is used as a stimulus for interferon production, the viability of the CrmA expressing cells is increased by about 60%. The ordinary artisan would expected that a 60% increase in cell viability will result in an increase of about 60% of interferon production. This is the result shown in Figure 2, thus the specification does not establish an unexpected result. Figure 4 and 5 compare the viability and interferon production of cells expressing Bcl-Xl (an anti-apoptotic gene) and PKR (6A) with cells expressing PKR only (A9). Here infection with a virus results in an increased viability of cells expressing Bcl-Xl (an anti-apoptotic gene) and PKR (6A) when compared to cells expressing only PKR (A9). The control that is missing in this figure and in the specification is the cell viability when expressing Bcl-Xl only. From the viability chart in figure 4A, after stimulation with a virus, it appears that cells expressing both Bcl-Xl (an anti-apoptotic gene) and PKR the cell viability are increased by about 20-25%. From the viability chart in figure 4A, after stimulation with a virus, it appears that cells expressing only PKR the cell viability are increased by about 5%. The ordinary artisan would expect that interferon production after stimulation by the virus would be roughly the same. In figure 5 the results have been presented in such a way that does not allow for a comparison. Here the interferon expression from wild

type cells have been assigned a value of zero. Wild type cells when stimulated with a virus will produce some interferon, the level is not zero (see figure 2). Figure 5A shows an interferon production that shows the same patterns as seen in cell viability after stimulation by the virus shown in Figure 4A. The pattern that is observed is that as cell viability increases so does the production of the useful compound. Upon careful review of the instant specification, the examples do not establish an unexpected result. Therefore applicants argument that there is no suggestion of the advantages obtained by the combination is not convincing.

In response to applicants argument that the logic of *In re Kerkhoven* is inapt because the Dixit or Suzuki reference have not actually demonstrated that transformation of a cell line with an anti-apoptotic protein does in fact enhance cytokine production. The prior art is not required to have actually made (reduced to practice) and used the composition for the same instantly claimed intended purpose. The prior art only needs two show that they have enabled one of ordinary skill to make the compositions. In this instance the prior art has actually made cell lines by inserting an anti-apoptotic gene into the cell, CrmA containing cells (Dixit) or Bcl-2 containing cells (Suzuki). These cells lines have been tested for viability and have been shown to have had increased viability when presented with an apoptotic stimulus. The apoptotic stimulus used are low serum culture conditions (Suzuki) or by binding of a ligand to a cell surface receptor (Dixet). These references have not tested the same cell lines for the production of cytokine after stimulation by a virus. Since the references were applied in a 35 USC 103 rejection the references only need to teach or suggest the instantly claimed invention. It remains the position of the Office that this teaching has been established in the instant rejection as well as the rejection made in the prior Office actions.

The mere recitation of newly-discovered function or property, inherently possessed by things in the prior art, does not cause the claim drawn to those things to distinguish over the prior art (See *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977), *In re Schreiber* 44 USPQ2d 1429). The prior art discloses CrmA containing cells (Dixit) or Bcl-2 containing cells (Suzuki), these cells would show increased survival if stimulated to produce interferon by addition of a virus, such as Sendai, ECMV, herpes or any other virus.

The claims have been amended in the response filed August 22, 2005. The instant invention is drawn to a composition, a cell line (claim 1) that is used for the production of a cytokine. The human cell composition comprising two-expression vectors, one vector expresses an anti-apoptotic gene and the other vector expresses a sequence encoding PKR. The additional descriptive language in the claims, that the level of cytokine production is greater or that Sendai virus induces interferon alpha production, does not further define the structure of the composition itself. The instant specification [page 25, lines 15-19] sets out that viral induced cytokine production is not limited to a specific virus. Thus the newly added limitation is merely a statement of intended purpose or intended results (that the composition produces greater cytokine production when exposed to Sendai virus) does not structurally add to the limitation of the composition. The claimed cell line expresses a coding sequence for an anti-apoptotic protein, specifically CrmA (claims 2). The claim language is only a statement of purpose and intended result.

It remains the Offices position that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the antiapoptotic protein CrmA with the PKR cell line. The prior art has shown that individually a cell line expressing PKR or an anti-

apoptotic protein are capable of overexpressing cytokines (products). Suzuki et al. suggests the use of combining an apoptosis-suppressive gene including CrmA for the production of cytokines and Lau teaches that the PKR cell line can overexpress a cytokine. One having ordinary skill in the art would have been motivated to include CrmA with the PKR cell line because both can be used for the expression of proteins (cytokines), as taught by Lau and Suzuki et al. Therefore, the instant invention is obvious over of Dixit, Lau et al. and Suzuki et al.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of

such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D
PRIMARY EXAMINER 11/4/05